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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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HUNT, J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/350,518	Reed et al.
Examiner	**Art Unit**
Jennifer Hunt	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 30, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-16, 19-27, 29-44, and 46* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-16, 19-27, 29-44, and 46* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *11*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

Response to Amendment

1. Acknowledgment is made of applicant's cancellation of claims 47-49. Claims 1-16, 19-27, 29-44 and 46 are pending in the application and considered herein.

Claim Rejections Withdrawn

2. All rejections of claims 47-49 are withdrawn in light of the cancellation thereof.

3. The rejection of claim 23 as containing subject matter which was not properly described in the specification is withdrawn in light of the arguments and evidence presented by applicant.

Claim Rejections Maintained

4. The rejection of claims 1-15, 38-43, and 46-49 for being enabling for detecting increased BAG-1 (*the truncated form taught in Takayama et al., Cancer Research, Vol 38, page 3116, abstract*) as an indicator of increased overall survival or distant metastasis free survival in Stage I or Stage II breast cancer patients, but not for detection of an increase or decrease in any and all BAG gene expressions as an indicator of prognosis, risk of recurrence, risk of metastasis, or monitoring treatment effectiveness for any and all cancer, is maintained for reasons of record.

In summary, the argument of the previous Office Actions sets forth that the specification discloses that increased levels of BAG-1 gene expression detecting using a monoclonal antibody

to the isoform BAG-1 (a truncated form of the full protein) predicts increased overall survival or distant metastasis free survival in patients with Stage I or Stage II breast carcinoma. Claims 1-15 are drawn to detection of any cancer, and claims 16, 18-27, 29-37, and 44 are drawn specifically to breast cancer in general. The claims also recite methods of detection of a decrease in BAG gene expressions as an indicator of increased risk of metastasis or recurrence for any and all cancer.

The prior art teaches that in many cancers, increased BAG expression is correlated with poor prognosis and increased risk of distant metastasis and tumor recurrence. *Tang et al., Journal of Clinical Oncology, Vol 17, No 6, pages 1710-1719, (June 1999)* teaches that increased BAG-1 expression was significantly associated with shorter disease free and overall survival in all stages of breast cancer (table 4, page 1718). Further, *Zapata et al., Breast Cancer Research and Treatment, Vol 47, pages 129-140 (1998)* teaches that BAG-1 levels are higher in invasive breast cancers (page 138, 1st column, 3rd paragraph). *Yawata et al., Oncogene, Vol 16, pages 2681-2686 (1998)* teaches that increased BAG-1 levels promote metastasis in colon cancer (abstract and page 2681, 2nd column, last paragraph). Additionally, *Takaoka et al., Oncogene, Vol 14, pages 2971-2977* (1997) teaches that over expression of BAG-1 promotes pulmonary metastasis of melanoma (abstract).

Therefor the art teaches that increased levels of BAG expression do not indicate decreased risk of metastasis or recurrence for any and all cancers, and likewise that decreased levels of BAG expression do not indicate increased risk of metastasis or recurrence for any and

all cancers. Similarly, detection of the different isoforms of BAG have lead to differing conclusions about breast cancer prognosis. Thus because the art sets forth specific examples in which the full scope of the instant claims are not enabled, one of ordinary skill in the art at the time the invention was made would not have been enabled to practice the full scope of the claimed invention.

Applicant's arguments are summarized herein:. (1) Applicant notes that claims 16, 18-27, 29-37, and 44 require that the cancer detected is breast cancer. (2) Applicant argues with regard to the references cited that the references do not accurately reflect the correlation between BAG-1 levels and prognosis, recurrence, or metastasis. (2a) Specifically, applicant argues that *Tang et al., Journal of Clinical Oncology, Vol 17, No 6, pages 1710-1719, (June 1999)* uses a polyclonal antibody, while the instant application uses a monoclonal antibody, and that using a polyclonal antibody may result in non-specific signals leading to erroneous detection of BAG-1 levels. Further, it is applicant's position that the statistical analysis done in Tang et al. is "prone to bias" because Tang et al. uses a heterogenous sample population and treatments, while the instant application uses a well defined sample population and uniform treatment. Applicant thus concludes that Tang et al. does not accurately reflect the correlation of BAG expression with prognosis of disease free or overall survival in a cancer patient. (2b) With regard to *Zapata et al., Breast Cancer Research and Treatment, Vol 47, pages 129-140 (1998*), applicant argues that the relationship between increased BAG-1 levels and invasive cancer was not significant. Applicant further argues that Zapata et al. states that no quantitative relationship between normal

and malignant breast tissue should be inferred. Applicant last speculates that the tumor samples of Zapata et al. are heterogenous, and thus are not reliable. (2c) With regard to *Yawata et al., Oncogene, Vol 16, pages 2681-2686 (1998)* and *Takaoka et al., Oncogene, Vol 14, pages 2971-2977* (1997) applicant merely states that these papers do not address breast cancer. (3) With regard to claims 1-15 and 38-43, drawn to methods of detecting cancer and kits for such, applicant reiterates arguments regarding the post filing declaration, and generic teachings in the specification, which allege that BAG-1 is "detectable" in prostate cancer, and thus based on the results obtained in the STAGE I and II breast cancer patients, is diagnostic for cancer in general. Applicant's arguments filed 4-30-2001 have been fully considered but they are not persuasive.

Initially, it is noted that applicant has not limited the claims to the enabled scope. As set forth in the previous office actions, and reiterated above, the teachings of the art are contrary to the instantly claimed invention. The art teaches that in breast cancer, as well as in melanoma, colon cancer, etc., that over expression of BAG-1 correlates with poor prognosis and decreased survival, which is contrary to the instant claims. Thus minimally, the art cited establishes a high level of unpredictability of correlations from BAG-1, and demonstrates that the instant assay would only function under specific conditions which are not instantly claimed.

With regard to argument (1), as noted above, claims 1-15, and 38-43 are generic to any type of cancer, while claims 16, 18-27, 29-37, and 44 require that the cancer detected is breast cancer.

With regard to the arguments of (2a), applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the detection of BAG-1 using a monoclonal antibody, or a homogenous sample and treatment population) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Genus*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, applicant has made many assertions in the absence of evidence (ie: that the assay is not accurate because it uses polyclonal antibodies and heterogenous populations). Arguments in the absence of evidence are not persuasive.

With regard to the arguments of (2b), applicant has cited a section of the paper, referring to one figure, and has not cited the ultimate conclusions drawn, nor the abundance of additional data which does lead to the correlation of increased BAG-1 levels and cancer detection (see for example, table 3). The section of the citation which was omitted by applicant makes it clear that the "caution that no quantitative relations between normal and malignant breast tissue should be inferred" refers specifically, and exclusively to the data of figure 2, which contains only 4 samples, unlike the abundance of other samples and assays which were performed.

With regard to the arguments of (2c), the examples of Yawata et al. and Takaoka et al. clearly set forth both the unpredictability of BAG-1 gene correlation to cancer detection, and are not addressed by applicant because they do not refer to breast cancer. The references are highly pertinent to the predictability of claims 1-15 and 38-44, and further support the conclusions of

Zapata et al. and Yawata et al. because they support that use of BAG-1 detection to diagnose or determine prognosis for breast as well as other cancers is clearly unpredictable.

With regard to the argument (3), as set forth above, applicant's arguments are not commensurate in scope with the claims, and further with regard to applicant's declaration, the declaration describes a single type of cancer where increased levels of BAG are associated with increased risk of tumor recurrence. The disclosure fails to teach this association, or to address the relationship of BAG levels to prostate cancer at all, absent a listing of prostate cancer among other cancers as potential candidate for a similar assay. Therefor, as set forth in the previous office action with regards to claims 1-16, 18-44 and 46, there is insufficient support under 35 U.S.C. 112 first paragraph for the full scope of the claims.

5. The rejection of claims 1, 3-4, 6-11, 13-15, 42-43, and 46 under 35 U.S.C. 102(b) as being anticipated by Zapata et al. is maintained for reasons of record.

Applicant argues that Zapata et al. fails to teach a method for determining prognosis of disease free or overall survival, citing specifically a section where Zapata et al. teaches that resistance to apoptosis in breast cancer lines is difficult to predict and thus applicant alleges that Zapata et al. teaches away from the instant invention. Applicant's arguments filed 4-30-2001 have been fully considered but they are not persuasive.

The section of Zapata et al. cited by applicant teaches there are many factors in determining resistance to apoptosis in breast cancer cells, but does not question BAG's

correlation to prognosis, which was set forth by statistically significant test results. As set forth in the previous office action, Zapata et al. teaches that there is a statistically significant correlation between BAG-1 immunostaining an invasive cancer, which is known to have a poorer prognosis (and is thus a prognosis for disease free or overall survival).(see 137, first full paragraph).

6. The rejection of claims 1, 3-4, 6-15, 38-43, and 46 under 35 U.S.C. 103(a) as being anticipated by Zapata et al., in view of Sano et al. is maintained for reasons of record.

Applicant's arguments regarding Zapata et al. Are addressed supra. Applicant further argues that Sano et al. fails to overcome the deficiencies of Zapata et al. Applicant's arguments filed 4-30-2001 have been fully considered but they are not persuasive.

This argument is rendered moot, as set forth above, since the rejection over Zapata et al. has been maintained.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly

signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

July 8, 2001

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